

5

## NEW TRICYCLIC COMPOUNDS

### BACKGROUND OF THE INVENTION

#### Field of the Invention

10        This invention relates to novel pharmaceutical  
tricyclic compounds, pharmaceutical compositions  
containing them and methods for their use and methods  
for preparing these compounds. In particular, it  
relates to tricyclic 5-HT<sub>3</sub> receptor antagonists  
15        containing a bridged bicyclic amine substituent. The  
invention also relates to novel intermediates for making  
the new tricyclic compounds.

#### Background of The Invention

20        Compounds with highly selective actions on 5-HT  
(serotonin or 5-hydroxytryptamine) receptor subtypes  
show clear potential for therapeutic benefit and provide  
tools with which scientists can better understand the  
role of 5-HT in disease. A number of different 5-HT  
25        receptor subtypes have been identified. Some of these  
are designated as 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors.  
Certain compounds having 5-HT<sub>3</sub> receptor mediating  
activity are useful for treating emesis, CNS disorders,  
cognitive performance disorders, drug dependency  
30        disorders, pain (e.g. migraine), cardiovascular  
disorders and gastrointestinal disorders. See, for  
example, an article entitled "Drugs Acting On  
5-Hydroxytryptamine Receptors" appearing in The Lancet  
September 23, 1989.

35

Novel tricyclic compounds have now been discovered  
that are useful inter alia for treating a variety of  
conditions influenced by the 5-HT<sub>3</sub> receptor. The  
compounds of this invention are active at very low  
5 levels, particularly in the treatment of emesis but show  
also activity in the treatment of other disorders as  
shown below.

10

15

20

25

30

35

2. The compound of Claim 1 wherein  
p is 0, 1 or 2;  
n is 1 or 2;  
q is 0;  
R<sup>1</sup> is halogen, lower alkoxy or amino;  
and if R<sup>3</sup> comprises  
R<sup>4</sup> and R<sup>5</sup>, they are each lower alkyl.
3. The compound of Claim 2 wherein n is 1.
4. The compound of Claim 3 wherein p is 0, the  
dashed line represents a double bond and if R<sup>3</sup> comprises  
R<sup>4</sup> and R<sup>5</sup> they are each methyl.
5. The compound of Claim 2 or 4 wherein R<sup>3</sup> is  
1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or  
endo-1-azabicyclo[3.3.1]non-4-yl.
6. The compound of Claim 5 wherein R<sup>3</sup> is  
1-azabicyclo[2.2.2]oct-3-yl, namely  
2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-  
cyclopent[de]isoquinolin-1-one.
7. The compound of Claim 6 which is 2-(1-  
azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-  
cyclopenta[de]isoquinolin-1-one hydrochloride.

8. The compound of Claim 6 which is  
(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-  
cyclopenta[de]isoquinolin-1-one hydrochloride.

5 9. The compound of Claim 5 wherein R<sup>3</sup> is  
8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely,  
2-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-  
1,2,4,5-tetrahydro-cyclopent[de]isoquinolin-1-one.

10 10. The compound of Claim 9 wherein R<sup>3</sup> is  
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely,  
2-(endo-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-  
1,2,4,5-tetrahydro-cyclopent[de]isoquinolin-1-one.

15 11. The compound of Claim 2 wherein n is 2.

12. The compound of Claim 11 wherein p is 0, the  
dashed line represents a double bond and if R<sup>3</sup> comprises  
R<sup>4</sup> and R<sup>5</sup>, they are each methyl.

20 13. The compound of Claim 12 wherein R<sup>3</sup> is  
1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
25 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or  
endo-1-azabicyclo[3.3.1]non-4-yl.

30 14. The compound of Claim 13 wherein R<sup>3</sup> is  
1-aza-bicyclo[2.2.2]oct-4-yl, namely  
2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-  
1H-benz[de]isoquinolin-1-one.

35

15. The compound of Claim 13 wherein R<sup>3</sup> is *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(*exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.
- 5 16. The compound of Claim 13 wherein R<sup>3</sup> is *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.
- 10 17. The compound of Claim 13 wherein R<sup>3</sup> is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.
- 15 18. The compound of Claim 17 which is (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.
- 20 19. The compound of Claim 17 which is (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one as the free base.
- 25 20. The compound of Claim 17 which is (*R*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.
- 30 21. The compound of Claim 13 wherein R<sup>3</sup> is *endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl, namely 2-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.
- 35

22. The compound of Claim 13 wherein  $R^3$  is  
*endo*-1-azabicyclo[3.3.1]non-4-yl, namely  
2-(*endo*-1-azabicyclo[3.3.1]non-4-yl)-2,3,5,6-tetrahydro-  
1*H*-benz[de]isoquinolin-1-one.

5

23. The compound of Claim 2 wherein  $p$  is 0, the  
dashed line represents two hydrogens, and if  $R^3$  comprises  
 $R^4$  and  $R^5$ , they are each methyl.

10

24. The compound of Claim 23 wherein  $R^3$  is  
1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
15 *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or  
*endo*-1-azabicyclo[3.3.1]non-4-yl.

25. The compound of Claim 24 wherein  $n$  is 1.

20

26. The compound of Claim 24 wherein  $n$  is 2.

25

27. The compound of Claim 26 wherein  $R^3$  is  
1-azabicyclo[2.2.2]oct-3-yl, namely  
2-(1-azabicyclo-[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-  
1*H*-benz[de]isoquinolin-1-one.

30

28. The compound of Claim 1 wherein  
 $n$  is 3;  
 $p$  is 0, 1 or 2;  
 $q$  is 0;  
 $R^1$  is halogen, lower alkoxy or amino;  
and if  $R^3$  comprises  
 $R^4$  and  $R^5$ , they are each lower alkyl.

35

29. The compound of Claim 28 wherein p is 0, the dashed line represents a double bond, and if R<sup>3</sup> comprises R<sup>4</sup> and R<sup>5</sup>, they are each methyl.

5        30. The compound of Claim 29 wherein R<sup>3</sup> is  
         1-azabicyclo[2.2.2]oct-3-yl;  
         1-azabicyclo[2.2.2]oct-4-yl;  
         endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
         endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
10        exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or  
         endo-1-azabicyclo[3.3.1]non-4-yl.

         31. The compound of Claim 30 wherein R<sup>3</sup> is  
         1-azabicyclo[2.2.2]oct-3-yl, namely  
15        (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-  
         hexahydrocyclohept[de]isoquinolin-1-one.

         32. A pharmaceutical composition comprising a  
therapeutically effective amount of a compound of  
20        Claim 1 to 31 or 40 to 43, preferably in combination  
         with a pharmaceutically acceptable excipient.

         33. A method for treating a condition chosen from  
emesis, a gastro-intestinal disorder, CNS disorder, a  
25        cardiovascular disorder and pain in an animal in need of  
         such treatment, which method comprises administering a  
therapeutically effective amount of a compound of  
Claim 1 to 31 or 40 to 43 or a composition of Claim 32  
to such animal.

30        34. The method of Claim 33 wherein the condition  
         is a gastrointestinal disorder.

35

35. The method of Claim 33 wherein the condition is a CNS disorder.

5 36. The method of Claim 33 wherein the condition is a cardiovascular disorder.

37. The method of Claim 33 wherein the condition is pain.

10 38. A method of treating emesis in a human undergoing cancer treatment using a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, which method comprises administering an anti-emetic amount of compound of Claim 1 to 31, 40 to 43, or a composition of Claim 32 to such human.

15 39. A method for treating an animal having a condition in which the 5-HT<sub>3</sub> receptor plays a role, which method comprises administering a therapeutically effective amount of a compound of Claim 1 to 31 or 40 to 43 or a composition of Claim 32 to such animal.

40. The N-oxide of the compound of Claim 1.

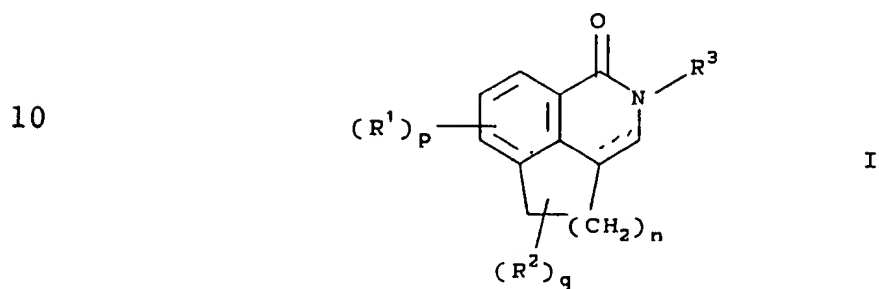
25 41. The compound of Claim 40 wherein  
p is 0, 1 or 2;  
q is 0;  
R<sup>1</sup> is halogen, lower alkoxy or amino;  
and if R<sup>3</sup> comprises  
30 R<sup>4</sup> and R<sup>5</sup>, they are each lower alkyl.

42. The compound of Claim 41 wherein p is 0, and if R<sup>3</sup> comprises R<sup>4</sup> and R<sup>5</sup>, they are each methyl.

35

43. The compound of Claim 42 wherein n is 2 and R<sup>3</sup> is 1-azabicyclo[2.2.2]oct-3-yl.

44. A process for the preparation of a compound of  
5 Formula I



15 in which

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

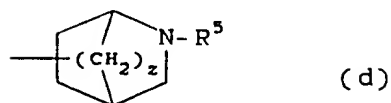
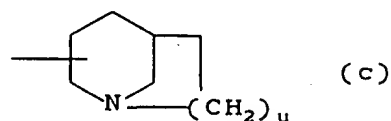
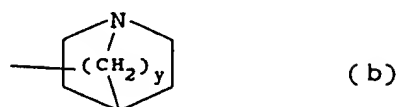
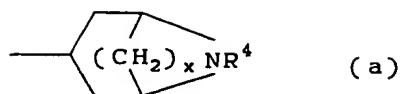
q is 0, 1 or 2;

20 each R<sup>1</sup> is independently selected from halogen, hydroxy, lower alkoxy (optionally substituted with phenyl), lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

25 each R<sup>2</sup> is lower alkyl; and  
R<sup>3</sup> is selected from

30

35



15 in which

u, x, y and z are all independently an integer from 1 to 3; and

20 R<sub>4</sub> and R<sub>5</sub> are independently C<sub>1-7</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyl-C<sub>1-2</sub> alkyl, or a group (CH<sub>2</sub>)<sub>t</sub>R<sub>6</sub> where t is 1 or 2 and R<sub>6</sub> is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two

25 substituents selected from C<sub>1-4</sub> alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C<sub>1-4</sub> alkyl (optionally substituted by hydroxy, C<sub>1-4</sub> alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable

30 acyloxy); or a pharmaceutically acceptable salt thereof or an *N*-oxide thereof, or an individual

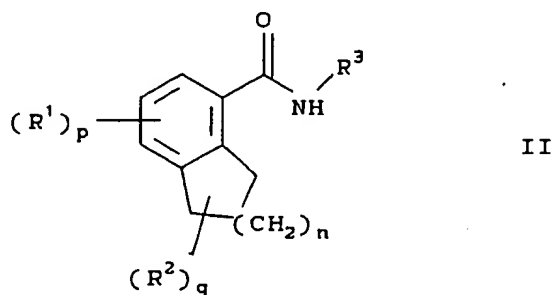
35

isomer or mixture of isomers thereof, which process comprises one or more of the following steps:

(a) reactively contacting a compound of Formula II

5

10



in which  $n$ ,  $p$ ,  $q$ ,  $R^1$ ,  $R^2$ , and  $R^3$  are as defined above with a formylating agent in the presence of a strong base to form a compound of Formula I wherein the dashed line is a double bond,

(b) reducing the double bond represented by the dashed line in Formula I by hydrogenation to form a compound of Formula I wherein the dashed line represents 2 hydrogens,

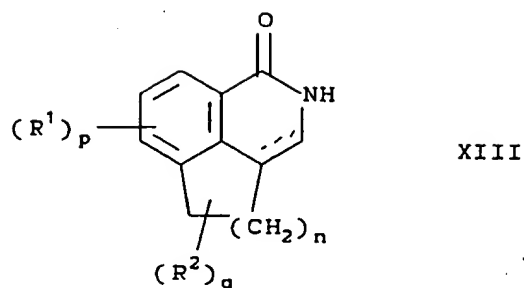
(c) converting a salt of a compound of Formula I to the corresponding free compound,

(d) condensing a compound of the formula  $R^3L$ , wherein  $R^3$  has the above meanings and  $L$  is a leaving group with a compound of the Formula XIII,

30

35

5



10 wherein  $R^1$ ,  $R^2$ ,  $n$ ,  $p$ ,  $q$ , and the dashed line have the above meanings,

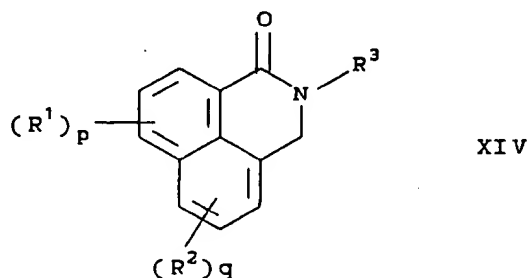
(e) converting a compound of Formula I to the corresponding pharmaceutically acceptable salt,

15 (f) oxidizing a compound of Formula I to form the corresponding *N*-oxide of the  $R^3$  component of Formula I, or reducing an *N*-oxide of the  $R^3$  component to the corresponding amine,

20 (g) reducing a  $R^1$  nitro substituent to a  $R^1$  amino substituent or alkylating or acylating a  $R^1$  amino substituent or alkylating a  $R^1$  hydroxy substituent or dealkylating a  $R^1$  alkoxy substituent or debenzylating a  $R^1$  benzyloxy substituent to the corresponding compound of Formula I,

25 (h) hydrogenating in positions 3a, 4, 5 and 6 a compound of the Formula XIV

30



35

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $p$  and  $q$  have the above meanings,

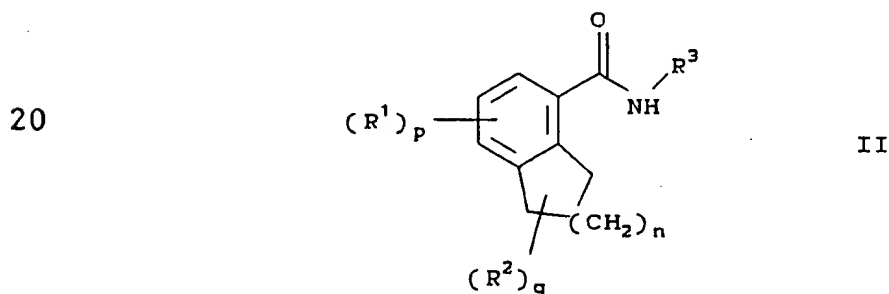
(i) separating a mixture of isomers or diastereomers of a compound of Formula I into a single isomer or a diastereomer, or

5 (j) conducting any of steps (a) through (i) with optically active reactants.

45. A process according to Claim 44 wherein  $R^3$  is selected from the group consisting of

10 1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; and  
endo-1-azabicyclo[3.3.1]non-4-yl.

15 46. A compound represented by the formula



25 wherein

$n$  is 1, 2 or 3;

$p$  is 0, 1, 2 or 3;

$q$  is 0, 1 or 2;

30 each  $R^1$  is independently selected from halogen, hydroxy, lower alkoxy (optionally substituted with phenyl), lower alkyl, nitro, amino, amino

35